Complete Summary

GUIDELINE TITLE

Naltrexone for the management of opioid dependence.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Naltrexone for the management of opioid dependence. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 28 p. (Technology appraisal guidance; no. 115).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Opioid dependence

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Pharmacology
Psychiatry
Psychology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Substance Use Disorders Treatment Providers

GUIDELINE OBJECTIVE(S)

- To undertake a systematic review of the clinical effectiveness of oral naltrexone for helping to prevent formerly opioid dependent people from returning to illicit drug use
- To systematically review enhanced treatment packages designed to improve compliance with oral naltrexone treatment
- To review published economic evaluations and undertake a de novo cost-utility analysis of oral naltrexone
- To see whether the evidence allows particular subgroups of opioid users or particular settings or care packages to be identified in which oral naltrexone is likely to be more effective or cost-effective

It is *not* the purpose of this review to consider

- The use of naltrexone in detoxification
- The use of naltrexone for other conditions, e.g., in alcohol abuse
- The relative merits of maintenance versus abstinence methods for the treatment of opioid dependence
- Depot or other unlicensed preparations of naltrexone

TARGET POPULATION

Detoxified formerly opioid-dependent people (who have remained opioid free for at least 7 to 10 days)

INTERVENTIONS AND PRACTICES CONSIDERED

Naltrexone as part of a programme of supportive care

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Changes in illicit drug use
    - Drug-related morbidity
    - Drug-related mortality

    - Health-related quality of life
    - Proportion of individuals being maintained opioid-free
    - Concordance with and retention to treatment
    - Adherence to treatment, treatment drop out
    - Societal function
    - Criminal activity, (re-)incarcerations
    - Utilisation of health care system
    - Mean duration of treatment
    - Serious adverse effects of treatment
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Collaboration (see the "Availability of Companion Documents" field).

Search Strategy

Clinical Effectiveness Reviews

For the clinical effectiveness review the following sources were searched:

- Bibliographic databases: Cochrane Library (Wiley) 2005 Issue 2, MEDLINE(Ovid) 1966–July week 4 2005 and MEDLINE In-Process (Ovid) at 3 August 2005 , EMBASE (Ovid) 1980–2005 week 36 and CINAHL (Ovid) 1982–July week 5 2005 , PsycINFO (Ovid) 1967–August week 1 2005, Science Citation Index/Social Science Citation Index (Web of Science) 1970–6 September 2005
- Research registries of ongoing trials including National Research Register 2005 Issue 2 and Current Controlled Trials *meta*Register and Clinical Trials.gov as at August 2005
- Citations of relevant studies
- Relevant internet sources including specialist substance abuse sites

Searches were not limited by date. No language restrictions were applied. Details of search strategies may be found in Appendix 7 of the Assessment Report (see the "Availability of Companion Documents" field.)

Experts were also contacted.

Cost-Effectiveness Review and Modelling

Studies on costs, quality of life, and information to populate the decision analytic model were identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid) 1966–July week 4 2005, EMBASE (Ovid) 1980–2005 week 32, Cochrane Library (Wiley internet version) (NHS EED and DARE) 2005 issue 2, Office of Health Economics HEED database August 2005 issue
- Internet sites of national economic units

Searches were not limited by date except for the quality of life searches (2004 to 2005) due to the large volume of material retrieved. There were no language restrictions. Details of search strategies may be found in Appendix 8 of the Assessment Report (see the "Availability of Documents" field).

Experts were also contacted.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Controlled trials of use of oral naltrexone compared to any other relapse prevention strategy (pharmacological, psychosocial, etc.) without naltrexone in detoxified formerly opioid-dependent individuals in both arms
- Systematic reviews of analytical observational studies looking at adverse events or other outcomes, e.g., crime rates, for naltrexone use for the same indication
- Randomised controlled trials of any intervention designed to enhance compliance with naltrexone treatment with the same naltrexone regimen in both arms

Exclusion Criteria

- Studies of naltrexone treatment outside the licensed indications such as subcutaneous implants or parenteral depot preparations
- Studies of naltrexone use for alcohol dependence or other indication
- Case reports and case series

Outcomes

See the "Major Outcomes Considered" field above.

NUMBER OF SOURCE DOCUMENTS

Twenty six studies met the inclusion criteria: nine were randomised controlled studies (RCTs) of interventions to increase compliance with naltrexone and 17 were studies considering the effectiveness of naltrexone. Of the latter 17, one was

a systematic review, 13 were RCTs and three were controlled but non-randomised studies.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Collaboration (see the "Availability of Companion Documents" field.)

Data Extraction Strategy

Data were extracted onto agreed pro-forma by two reviewers independently. Results were extracted, where possible for intention-to-treat populations, as raw numbers, plus any summary measures with standard deviations, confidence intervals, and p-values. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

Quality Assessment Strategy

The quality of the clinical effectiveness studies were assessed according to criteria based on National Health Service Center for Review and Dissemination (NHS CRD) Report No. 4 by one reviewer and checked by a second reviewer. A Jadad score was used. This gave a score from 0 (poorest quality) to 5 (best quality). Disagreements were resolved by consensus and where necessary a third reviewer was consulted.

Data Analysis

The main results were placed in tables. Studies were grouped according to outcome and comparison groups. Where possible the results were summarised by calculating relative risks (including hazard ratios if appropriate) and risk differences with 95% confidence intervals for dichotomous outcomes. Meta-

analysis was carried out where appropriate. Analysis by subgroups (e.g., settings, patient characteristics) was explored.

Survival analysis for treatment retention rates was carried out in the following steps:

1. The treatment retention rates from primary studies were measured manually and linearly interpolated in weekly time points.
2. The combined survival analysis curves for the intervention group and the control group were generated by summing not-retention-treatment events of the primary studies at weekly time points and censoring patients who still retained in treatment at the end of follow-up of the studies.
3. The logarithm of the hazard ratios and their variances were obtained by performing log-rank test.
4. The pooled hazard ratio and its 95% confidence interval were derived by meta-analysing the individual hazard ratios using Equation 1 (see section 3.6 of the Assessment Report [see the "Availability of Companion Documents" field)

The same analysis was done for proportion who refrained from use of illicit drugs in each group.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and

commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

No published economic evaluations of the cost effectiveness of naltrexone treatment were identified. The manufacturer did not submit evidence for this appraisal.

The Assessment Group developed a decision analytical model to assess the cost effectiveness of naltrexone plus psychosocial support compared with placebo plus psychosocial support (psychosocial support alone). The model estimated costs and outcomes from a National Health Service (NHS) perspective. Costs were based on estimates of resource use including a daily dose of 50 mg naltrexone, counselling sessions, monitoring of treatment, general practitioner (GP) visits, emergency department visits, inpatient hospital stays, outpatient mental health appointments, and inpatient mental health admissions. The time horizon of the model was limited to 12 months. This was because of the length of follow-up in the trials, and clinical advice that people are not retained on naltrexone treatment in the long term.

See section 4.2 in the original guideline document for a detailed discussion of the Assessment Group's decision analytical model.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence programme.
- Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care.
- The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly. Discontinuation of naltrexone treatment should be considered if there is evidence of such misuse.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of naltrexone for the management of opioid dependence

POTENTIAL HARMS

- Naltrexone is associated with opioid withdrawal symptoms if people are opioid dependent. The Summary of Product Characteristics (SPC) recommends challenge testing with naloxone hydrochloride (a shorter-acting injectable opioid antagonist) to screen for the presence of opioids if it is not certain whether the person is detoxified. People may be at risk of a fatal overdose caused by respiratory depression if they relapse while taking naltrexone. This can happen if the person tries a larger dose of diamorphine to achieve euphoria, or if they return to diamorphine use after naltrexone treatment, because of loss of tolerance to diamorphine.
- Caution should be observed in administering naltrexone to patients with impaired hepatic or renal function.

For full details of side effects and contraindications, see the SPC available at http://emc.medicines.org.uk/.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation

- The Healthcare Commission assesses the performance of National Health Service (NHS) organizations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with

effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (www.nice.org.uk/TA115) (see also the "Availability of Companion Documents field).
    - A costing statement explaining the resource impact of this guidance.
    - Audit criteria to monitor local practice.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Naltrexone for the management of opioid dependence. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 28 p. (Technology appraisal guidance; no. 115).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jan

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Dr Darren Ashcroft, Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Professor David Barnett, Professor of Clinical Pharmacology, University of Leicester; Dr Peter Barry, Consultant in Paediatric Intensive Care, Leicester Royal Infirmary; Mr Brian Buckley, Lay Member; Professor John Cairns, Public Health and Policy, London School of Hygiene and Tropical Medicine; Professor Mike Campbell, Statistician, University of Sheffield; Professor David Chadwick, Professor of Neurology, Walton Centre for Neurology and Neurosurgery, Liverpool; Dr Mark Chakravarty, Industry Member; Dr Peter I Clark, Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside; Dr Mike Davies, Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary; Mr Richard Devereaux-Phillips, Industry Member; Professor Jack Dowie, Health Economist, London School of Hygiene; Dr Fergus Gleeson, Consultant Radiologist, The Churchill Hospital, Oxford; Ms Sally Gooch, Independent Healthcare Consultant; Mr Sanjay Gupta, Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust; Professor Philip Home, Professor of Diabetes Medicine, University of Newcastle upon Tyne; Dr Peter Jackson, Clinical Pharmacologist, University of Sheffield; Professor Peter Jones, Professor of Statistics & Dean Faculty of Natural Sciences, Keele University; Dr Mike Laker, Medical Director, Newcastle Hospitals NHS Trust; Dr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton; Ms Rachel Lewis, Nurse Advisor to the Department of Health; Mr Terence Lewis, Lay Member; Professor Jonathan Michaels, Professor of Vascular Surgery, University of Sheffield; Dr Neil Milner, General Medical Practitioner, Sheffield; Dr Ruairidh Milne, Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology; Dr Rubin Minhas, General Practitioner, CHD Clinical Lead, Medway PCT; Dr Rosalind Ramsay, Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London; Mr Miles Scott, Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust; Dr Lindsay Smith, General Practitioner, East Somerset Research Consortium; Mr Roderick Smith, Director of Finance, Adur, Arun and Worthing PCT; Dr Ken Stein, Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter; Professor Andrew Stevens, Professor of Public Health, University of Birmingham

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Naltrexone for the management of opioid dependence. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 2 p. (Technology appraisal 115). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Costing statement: naltrexone for the management of opioid dependence. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 2 p. (Technology appraisal 115). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Naltrexone for the management of opioid dependence. Audit criteria. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 12 p. (Technology appraisal 115). Available from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Oral naltrexone as a treatment for relapse prevention in formerly opioid dependent drug users: a systematic review and economic evaluation. Assessment report. West Midlands Health Technology Assessment Collaboration, University of Birmingham. 2006 Feb. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1176. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Naltrexone for managing opioid dependence. Understanding NICE guidance – Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 4 p. (Technology appraisal 115).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1177. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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